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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/268,610	06/06/1995	SIMON C. BURTON	010055-134	5415

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EXAMINER

WEBER, JON P

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 06/21/2002

26

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/468,610

Applicant(s)

BURTON ET AL.

Examiner

Jon P. Weber, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5,7-23,55 and 56 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-5,7-23,55 and 56 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ 6) ☐ Other:

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Situs of the Claims

The response with amendments and Becker Declaration filed 28 January 2002 and the response with amendments and Burton and Cramer Declarations filed 27 March 2002 have been received and entered.

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 24-26 been renumbered 55-56. Claims 1-5, 7-23 and 55-56 have now been presented for examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7-23 and 55-56 are rejected now under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 26-28 of U.S. Patent No. 5,652,348. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent claims are drawn to a resin for purifying proteins wherein the resin must meet the same requirements as the instant claims - at a first pH the resin is uncharged and the protein binds, at a second pH the resin is charged and the protein elutes. The patent claims are drawn to the resin alone rather than the complex of resin and protein. Given that the functional intended use is to purify proteins, it would be obvious that the complex is formed during the usage. The patent claims are broader than the instant claims. Boardman et al. (1953) (*vide infra*) was not cited during prosecution of the patent.

Claim Rejections - 35 USC § 112

Claims 55-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims assert that the ionizable ligand includes hydroxyl and thiol groups. It is clear from the paragraph bridging pages 14-15 that these two groups are reactive functionalities of the solid support matrix that permit covalent attachment of the ionizable ligand, not the ligand

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itself. In the first full paragraph at page 15 are listed the ionizable ligands which do not include these two functionalities. This is a new matter rejection. Appropriate correction is required.

Claim Rejections - 35 USC § 102

Claims 1-2, 4-5, 10-16, 18, 20 and 22-23 stand rejected under 35 U.S.C. 102(b) as being anticipated by Boardman et al. (1953).

A complex between an ion exchange resin and a target protein is claimed wherein the complex is formed at a pH value of between 5-9, where the resin is uncharged, and the target protein is bound to the resin by hydrophobic interactions. The ion exchange resin consists of a solid support matrix and a covalently attached ionizable ligand. The resin may further comprise non-ionizable ligands.

It is argued that Boardman et al. (1953) fails to teach forming a complex of the resin and the protein at a pH in the range of 5-9 and subsequently eluting within the same range. It is argued that the Declaration of Becker supports the position that the resin does not meet the claim limitation that the resin is uncharged at the pH where the protein is bound. Becker argues that the pKa of the resin is 6.1. A figure from the manufacturer's data sheet is provided to support the assertion that the resin supports a partial charge at pH value of 5.0. The Burton Declaration provides several arguments: actual vs theoretical titrations are compared, it is asserted that Boardman shows the matrix 20% ionized at pH 5.0, the Rohm and Haas data shows fully protonated only between 2.5 and 4.0. Burton indicates that the pKa of the resin in the titration is 6.2.

At page 18, first full paragraph, the specification recites:

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The term “electrostatically uncharged at the pH where the target protein is bound to the resin” means that less than 5% of the ionizable functionalities on the resin are charged at the pH of the target protein binding. Preferably, less than about 1% of the ionizable functionalities on the resin are charged at this pH.

The titrations in the Burton Declaration are pH vs meq of NaOH added. In Boardman et al. as well as in Topp et al., the titrations are pH vs sodium ion uptake. The relevant equations from Boardman et al. and Topp et al. are:

- (1) $HR + Na^+ \rightleftharpoons NaR + H^+$ for the sodium hydrogen exchange on the resin
- (2) $RH + P^+ \rightleftharpoons RH...P^+$
- (3) $RH...P^+ + Na^+ \rightleftharpoons R-Na^+ + P^+ + H^+$
- (4) $R-Na^+ + P^+ \rightleftharpoons R-P^+ + Na^+$

In Topp et al., the relevant data is presented at Figure 2 and discussed at page 3301. It is stated that in the absence of added salt, exchange is negligible at pH's below 6, but increase progressively up to a pH of 11. In the presence of 0.1 M NaCl, the uptake is greatly increased at intermediate values of pH. The ratio of $[Na^+]/[H^+]$ in solution must be greater than 10^8 for complete exchange of carboxylic hydrogen for sodium to occur. From Figure 2, at pH 5.0 the amount of sodium ions is about 0.3 mg equiv/dry g of resin in 0.1 M NaCl. That is, the resin is hardly ionized at pH value of 5.0 in 0.1 M NaCl. The half neutralization point is about 9.0 with no added salt, and about 7.0 with 0.1 M NaCl (see the discussion in Kitchener at page 63 to confirm this interpretation). This result is confirmed in Figure 1a of Boardman et al. At a pH value of 5.0, in 0.1 M sodium ions (B), the sodium uptake is negligible. Certainly, no added salt is low ionic strength as required by the instant claims.

Kunin provides similar titration data to the Burton Declaration, meq.OH/g dry resin vs pH in Figure 13. The data show titration in water, 0.01 M KCl and 0.1 M KCl. This is the same

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data presented by Rohm and Haas in the Becker Declaration. In water, at pH 5.0, there is apparently negligible effect. In 0.01 M KCl, at pH 5.0, about 0.7 meq have been added. Finally, in 0.1 M KCl, at pH 5.0, about 2 meq sodium ions have been a.

Hence, for the carboxyl group both salt concentration and pH affect the ionization state, although some variance occurs with the resin support. It is consistently seen that at low ionic strength, the properties of the carboxyl approach that of in water. The percent ionized is low at pH 5.0 in water or low ionic strength. The percent ionized increases with increased ionic strength. Specifically, Boardman et al. state at page 210, first full paragraph **“as is shown in Fig. 1a, at pH 5 the carboxylic groups of the resin are almost wholly undissociated,”** (this is not examiner’s interpretation as argued in the response). The assertion in the Burton declaration that Boardman et al. show that the resin is 20% dissociated at pH 5.0 only applies at high ionic strength (*vide infra*).

The Burton declaration shows that the actual titration was performed in 1 M NaCl added using CG-50 (said by Burton to be comparable to IRC-50 except for pore size). As can be seen from the various results shown in the references, increasing ionic strength shifts the ionization to lower pH values. That can be clearly seen in Boardman et al., Fig. 1a curve A, at 1 M NaCl, which shows that at pH 5.0 there are almost 2 meq of sodium bound at the beginning of the titration (just under 20% ionized as the resin capacity has been established as 10 meq/dry gram). Kunin also shows that increasing ionic strength increases the percent ionized at pH 5.0. Kunin points out that the full description of the titration curves needs to account for the activity coefficients of the ions (see the equations at page 39). As is known from physical chemistry, the activity coefficients approach unity in dilute solution ($[Na^+]$ goes to zero), the simple Henderson-

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Hasselbach equation would then hold. Hence, the deviation between the observed titration by Burton and the theoretical titration is a natural consequence of accounting for the activity of the ions in solution.

Accordingly, at the pH value of 5.0 where the protein, cytochrome C, is binding in Boardman et al. (1953), the resin meets the definition of “electrostatically uncharged” set forth in the specification at low ionic strength.

In conclusion, Boardman et al. (1953) disclose binding at a pH value where the resin is electrostatically uncharged, and elution at a pH value where the resin is charged, wherein these pH values are within the range required by the claims. A complex between protein and resin is formed in the critical range that meets the claims.

Applicant's arguments filed 28 January 2002 and 27 March 2002 have been fully considered but they are not persuasive. The rejection under 35 USC 102(b) is adhered to for the reasons of record and the additional reasons above.

N.B. The Cramer declaration only adds a concurring opinion, and no further data.

Claim Rejections - 35 USC § 103

Claims 1-5, 7-23 and 55-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boardman et al. (1953), Sasaki et al. (1979) and Sasaki et al. (1982) in view of Kunin (1958), Topp et al. (1949), Kitchener (1957) and Guthrie (1957) and further in view of Hancock et al. (US 4,401,629), Kitamura et al. (JP 01211543), Tokuyama (JP 60137441), Kondo et al. (JP 61033130), Iimuro et al. (US 4,950,807), Bruegger (US 4,810,391), Economy et al. (US 3,835,072), Jones et al. (US 4,154,676).

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The arguments re Boardman et al. (1953) are reiterated. It is argued that the secondary references fail to remedy the deficiency. It is urged that Sasaki et al. teach binding at pH 4.5. It is urged that the other references do not disclose resins that have binding properties in the critical pH 5-9 region. It is concluded that the Office action makes an improper obvious to try argument. In addition specific ion exchange ligands are claimed.

Hancock et al. (US 4,401,629) disclose polymeric ion exchange resins comprising a cross-linked vinyl backbone with attached imidazolyl groups optionally substituted with pyridyl, imidiazolyl or amino groups (see abstract).

Kitamura et al. (JP 01211543), Kondo et al. (JP 61033130) or Iimuro et al. (US 4,950,807) disclose polymeric ion exchange resins having pyridyl group as the exchange group.

Tokuyama (JP 60137441) or Bruegger (US 4,810,391) disclose ion exchange resins which may have phenolic hydroxyl group as the exchange group.

Economy et al. (US 3,835,072) discloses ion exchange fibers which may have a primary, secondary, tertiary or quaternary amino group as the exchange group (column 1, lines 67-72).

Jones et al. (US 4,154,676) disclose polymeric ion exchange resins having the morpholino (column 2) group *inter alia* as the exchange group.

The teachings of Boardman et al. (1953) have been discussed in full above. Clearly, Boardman et al. (1953) teach a resin with binding properties in the critical region. Sasaki et al. references were cited because they clearly disclose the concept of the instant invention. The cartoon of Figure 5 in Sasaki et al. (1982) outlines the method in its most general form. The cartoon illustrates an acidic group undergoing ionization. At low pH the proteins absorb to the uncharged resin by hydrophobic effects. As the pH is raised, the resin becomes charged and the

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proteins elute. The figure legend goes on to say that the method “can be used with an absorbent carrying alkaline groups, although the relationship to pH would be the opposite”. That is, at high pH the resin is uncharged and the proteins bind by hydrophobic effects. As the pH is lowered, the resin becomes charged and the proteins elute. Sasaki et al. only illustrates the method with a resin that binds at pH 4.5. It is clear that their conceptualization only requires that there be resins which bind in the critical region of 5-9.

In Kunin (1958), for example, the titration curves for salt exchange were used to calculate the apparent ionization constants of some acidic resins. These are listed at page 35. In Topp et al. (1949) it is clear, for example, that the carboxyl group of polymethacrylate (Figure 2) undergoes salt exchange in the region of 6-9 in the absence of added salt (this is further discussed at page 3301, first full paragraph). The values for pKa can be compared to the values for pKa for suitable resins given in the instant disclosure on Tables 3 and 4 (alkaline and acid resins respectively). It would appear that suitable resins are relatively easy to obtain. There is nothing obvious to try at all. The references clearly lead to using suitable resins in the allegedly critical region of pH. Such resins are clearly known in the art and reasonably suggested by Hancock et al. (US 4,401,629), Kitamura et al. (JP 01211543), Tokuyama (JP 60137441), Kondo et al. (JP 61033130), Iimuro et al. (US 4,950,807), Bruegger (US 4,810,391), Economy et al. (US 3,835,072), Jones et al. (US 4,154,676). These latter references disclose resins containing ionizable ligands as the exchange groups alleged to be suitable and specifically claimed as such in claims 55-56.

Applicant's arguments filed 28 January 2002 have been fully considered but they are not persuasive. The rejection under 35 USC 103 is adhered to for the reasons of record and the additional reasons above.

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Other references cited by examiner but not relied upon are cited to establish the state of the art or are cumulative of information in references relied upon.

No claims are allowed.

Applicant's action necessitated the new ground of rejection under Double Patenting presented in this Office action based upon applicants' own issued patent, which Examiner only recently discovered. Consider the reasoning set forth in MPEP 609 regarding information disclosure statements filed after the First Office action on the merits but prior to a final Office action, i.e., during the period set forth in 37 CFR 1.97(c).

i) Final Rejection is Not Appropriate

If information submitted during the period set forth in 37 CFR 1.97(c) with a statement under 37 CFR 1.97(e) is used in a new ground of rejection on unamended claims, the next Office action will not be made final since in this situation it is clear that applicant has submitted the information to the Office promptly after it has become known and the information is being submitted prior to a final determination on patentability by the Office.

ii) Final Rejection is Appropriate

The information submitted with a statement under 37 CFR 1.97(e) can be used in a new ground of rejection and the next Office action can be made final, if the new ground of rejection was necessitated by amendment of the application by applicant. Where the information is submitted during this period with a fee as set forth in 37 CFR 1.17(p), the examiner may use the information submitted, and make the next Office action final whether or not the claims have been amended, provided that no other new ground of rejection which was not necessitated by amendment to the claims is introduced by the examiner.

See MPEP § 706.07(a).

The implication of these statements is clear. When art is newly discovered by applicant and they promptly submit such art to the Office, then any new ground of rejection based upon

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such art will not be made final. However, if applicant knows of art but fails to submit it promptly, then any new ground of rejection based on such art can properly be made final.

Here applicants clearly knew of their own issued patent, long before it was made of record by examiner and relied upon in a rejection. There does not appear to be any indication in the record that applicants have made any attempt to bring the issued patent to the attention of the Office. The result of applicants' failure to disclose to the Office a reference known to them should not benefit applicants with a non-final Office action, when one who complies with the duty to disclose under 37 CFR 1.56 by filing an information disclosure statement under 1.97(c) with the appropriate fee would not get such benefit. Therefore based on the facts in this situation and the reasoning of section 609 of the MPEP, it is determined that it is applicants' action, or lack thereof, which resulted in the new ground of rejection.

The newly submitted claims required the addition of references establishing that such resins were known in the art. The new matter rejection is also based upon the newly submitted claims.

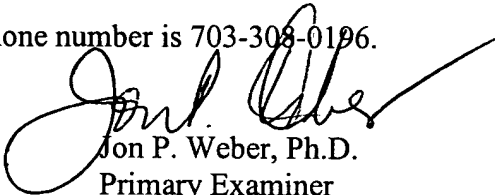
Accordingly, it is proper that **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P. Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Jon P. Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
June 18, 2002